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IP DEPARTMENT OF PIPER RUDNICK LLP
ONE LIBERTY PLACE, SUITE 4900
1650 MARKET ST
PHILADELPHIA, PA 19103

EXAMINER

KUBELIK, ANNE R

ART UNIT PAPER NUMBER

1638

DATE MAILED: 04/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/807,721

Applicant(s)

DANIELL ET AL.

Examiner

Anne R. Kubelik

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 December 2003 and 23 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 and 28-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 28-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

1. Claims 1-7 and 28-33 are pending.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. The objection to claims 1-7 and 28-33 because of informalities is withdrawn in light of Applicant's amendment of the claims.
4. The information disclosure statement filed 21 August 2003 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered. The PTO 1449 is missing.

Claim Rejections - 35 USC § 112

5. Claims 1-7 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plastid transformation vector that transforms tobacco, does not reasonably provide enablement for a plastid transformation vector that transforms any plant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the full enablement rejection set forth in the Office action mailed 6 June 2003 due to Applicant's amendment of the claims. Applicant's arguments filed 11 December 2003 have been fully considered but they are not persuasive.

The claims are broadly drawn to plastid transformation vectors comprising plastid DNA, a plastid promoter, a selectable marker sequence, a DNA encoding a portion of an

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immunoglobulin, and transcription termination region, and additional plastid DNA sequence and methods of using the vectors to transform plastids or any plant.

The instant specification, however, only provides guidance for construction of an tobacco plastid expression vector comprising an expression cassette comprising the Guy's 13 heavy chain variable region fused to the mouse IgA2m(2) constant region followed by the Guy's 13 light chain variable region fused to the human kappa constant region (example 1A); transformation of the vector into *E. coli* and analysis of its expression (example 1B); transformation of the vector into tobacco and analysis of the expression of the RNA and protein (examples 1C-F). The specification provides general guidance for Elisa Assay for testing the effectiveness of the antibody produced in the plastids (examples (G-H), and optimization of codon usage (example 2). The specification provides prophetic expression of a construct encoding an IgA heavy chain, a light chain, a J chain and a secretory component or encoding ICAM-1 in tobacco plastids (examples 3-5).

The instant specification fails to provide guidance for plastid transformation vectors comprising plastid DNA, a plastid promoter, a selectable marker sequence, a DNA encoding a portion of an immunoglobulin, and transcription termination region, and additional plastid DNA sequence, wherein the vectors have flanking sequences that allow the vector to be targeted to the genome of any higher plant chloroplast.

The region of the tobacco plastid genome commonly used for targeting of transformation vectors is not present in the same configuration or sequence in the genomes of other plastids. For example, rice lacks the orf131/orf70B gene (Kanno et al, 1993, Curr. Genet. 23:166-174;

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see Figure 3). The specification fails to teach a region of the plastid genome that is homologous across all higher plants.

The instant specification also fails to teach transformation of the plastids of any plant species other than tobacco. Heifetz (2000, *Biochimie* 82:655-666) teaches that reliable and efficient plastid transformation and regeneration of fertile plants with transformed plastids has been limited to tobacco and potato (pg 658, right column, paragraph 2).

As the specification does not describe the transformation of any plant with a plastid transformation vector comprising plastid DNA, a plastid promoter, a selectable marker sequence, a DNA encoding a portion of an immunoglobulin, and DNA encoding an chaperonin, and transcription termination region, and additional plastid DNA sequence, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants or algae transformed therewith, to identify those with that express immunoglobulin in their plastids, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, and lack of guidance in the specification as discussed above, the instant invention is not enabled.

Applicant urges that their claims are drawn to the vector, not to transformed plants as seems to be the focus of the rejection; the specification indisputably teaches how to construct a vector (response pg 9).

This is not found persuasive because part of the rejection focuses on Applicant's lack of teaching how to use the vector. Furthermore, claims 28-33 are drawn to methods of transforming the vectors into plant plastids. Lastly, the specification does not teach how to construct vectors within the full scope of the claims.

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Applicant urges that their teachings are not limited to their embodiment and that pg 16, lines 6-19, teach the use of a universal plastid expression-integration vector in which the flanking sequences are taught to be highly conserved among higher plants. Applicant urges that those of skill in the art would expect the claimed vector to be integratable into plastids of a wide variety of higher plant species (response pg 9).

This is not found persuasive because the claimed vectors are drawn to those with any region of homology to the plastid, not to those with a specific region. Additionally, as not all plants have even the exemplified region of homology, it is not clear in which plants the exemplified vector can be integrated.

Applicant urges that Heifetz does not dispute the fact that transformation vectors can integrate in a wide number of species but instead focuses on the fact that selection of transformed cells is the primary difficulty in regenerating transformed plants; thus Heifetz does not to refute the enablement for the construction of the claimed vectors (response pg 9-10).

This is not found persuasive because use of the vectors and production of plants with transformed plastids requires selection of transformed cells and regeneration of transformed plants; thus, Heifetz is relevant to the instant claimed vectors.

6. Claims 1-7 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action

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mailed 6 June 2003 due to Applicant's amendment of the claims. Applicant's arguments filed 11 December 2003 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of plastid transformation vectors comprising plastid DNA, a plastid promoter, a selectable marker sequence, a DNA encoding a portion of an immunoglobulin, transcription termination region, and additional plastid DNA sequence. In contrast, the specification only describes a single plastid transformation vector encoding the Guy's 13 heavy chain variable region fused to the mouse IgA2m(2) constant region followed by the Guy's 13 light chain variable region fused to the human kappa constant region. Applicant does not describe any other vectors encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described plastid transformation vectors comprising plastid DNA, a plastid promoter, a selectable marker sequence, a DNA encoding a portion of an immunoglobulin, and transcription termination region within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant urges that the rejection has been obviated by amendment to delete reference to a DNA encoding a chaperonin (response pg 10).

This is not found persuasive because Applicant does not describe vectors comprising plastid flanking sequences within the full scope of the claims.

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7. Claims 6 and 28-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated for the reasons of record as set forth in the Office action mailed 6 June 2003, as applied to claims 1-7 and 28-33. Applicant's arguments filed 11 December 2003 have been fully considered but they are not persuasive.

Claims 6 and 33 are indefinite in their recitation of "fused to an operative ligand".

Applicant urges that the rejection was addressed by amendment (response pg 10).

This is not found persuasive because it is unclear what the ligand is operative for and what the ligand is bound by. No amendment was made to address this rejection.

Claim 28 lacks antecedent basis for the limitation "said heterologous DNA" in lines 13-14.

Applicant urges that the rejection was addressed by amendment (response pg 10).

This is not found persuasive because no amendment was made to address this rejection.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 1-4, 6, 28-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over McBride et al (US Patent 6,512,162, filed July 1998) in view of Mayfield et al (WO 98/31823).

The claims are drawn to a plastid transformation vector comprising an expression cassette comprising a plastid promoter, a selectable marker sequence, a DNA sequence encoding a immunoglobulin, a termination signal, wherein the expression cassette is flanked by plastid sequences from a higher plant species, and a method of using it to transform plastids.

McBride et al disclose a plastid transformation vector comprising an expression cassette comprising a plastid promoter, a DNA sequence encoding a eukaryotic peptide, a termination signal, a second promoter, a selectable marker sequence and a second terminator, wherein the expression cassette is flanked by plastid sequences from a higher plant species (Figure 9) and methods of plastid transformation with the vector (column 17, line 22, to column 18, line 31; column 25, line 18, to column 28, line 14). McBride et al do not disclose vectors encoding an immunoglobulin or with the components in the exact order as claimed in the instant claim 1 and 28.

Mayfield et al teach vectors for transforming the plastids of the algae *Chlamydomonas*, wherein the vectors encodes a tetanus toxin single chain antibody and a dimeric IgA comprising heavy, light and J chains, and wherein the immunoglobulins are part of a polycistronic message (pg 76, line 22, to pg 80, line 31).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of plastid transformation as taught by McBride et al, to express DNAs encoding immunoglobulins as described in Mayfield et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Mayfield et al to produce these protein in plants (pg 76, line 29) and because of the advantages that expression in plastids provides (McBride et al, column 1, lines 65-67). Expression of the selectable marker and the

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immunoglobulin on the same construct is suggested by Mayfield et al, who tout the advantages chloroplasts provide for this (pg 78, line 21, to pg 79, line 16). The exact order of the components of the vectors is an obvious design choice. The light chain of the single chain antibody would be an "operative ligand".

10. Claims 1-6 and 28-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over McBride et al in view of Mayfield et al as applied to claims 1-4, 6, 28-31 and 33 above, and further in view of Christou et al (US 2002/0078472, filed June 1998).

The claims are drawn to plastid transformation vectors encoding an immunoglobulin light chain, heavy chain, single chain variable fragment, or a heavy chain fused to an operative ligand.

The teachings of McBride et al in view of Mayfield et al are discussed above. McBride et al in view of Mayfield et al do not disclose an scFv as the immunoglobulin.

Christou et al teach expression of the immunoglobulin scFV24, among others (§68- §119).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing immunoglobulins in the plastids of higher plants as taught by McBride et al in view of Mayfield et al, to use an scFv as the immunoglobulin as described in Christou et al. One of ordinary skill in the art would have been motivated to do so because Christou et al suggests targeting the immunoglobulin to the chloroplast (§20) and because selection of immunoglobulin as an obvious design choice.

11. Claim 7 is free of the prior art, given the failure of the prior art to teach or suggest a plastid transformation vector comprising a polycistron encoding heavy and light chains of an

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immunoglobulin, wherein the chains are separated by a linker comprising a stop codon and a ribosome binding site.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (571) 272-1600.

Anne R. Kubelik, Ph.D.
April 2, 2004

